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Itching for a Reason: Understanding Mechanisms of Itch

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Itching for a Reason: *Understanding Mechanisms of Itch*

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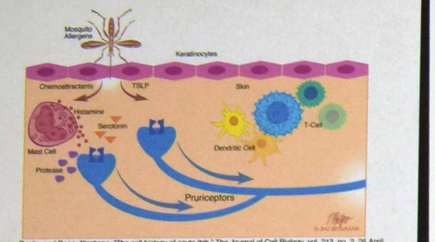

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Image: A variety of cell types interact as a response to itch stimuli (mosquito bite), ultimately inducing the release of histamine. Then, histamine binds to its receptor and the itch signal is transmitted to the spinal cord. Other cells like dendritic or T-cells also release other pruritogens like proteases.[2]

Non-neuronal Cells Contributing to Itch:

- Keratinocytes
  - Release thymic stromal lymphopoietin (TSLP) that activates their receptors (TSLPR) to induce itch
  - Release chemoattractants to recruit immune cells (like mast cells)
- Mast cells
  - Release histamine from granules that bind to their receptors, activating itch receptors and transmitting signals to spinal cord[2]

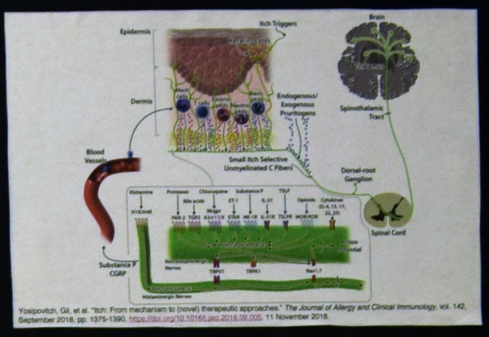
What is an itch?

- Almost everyone has experienced itchiness, or the "unpleasant sensation that elicits the desire or reflex to scratch"[4]
- Acute or chronic/severe (also known as pruritus)[1]
- Types include pruritoceptive (insect bites), neuropathic (neuronal damage), or psychogenic (psychiatric origins)[4]

Two major and distinct neuronal pathways to transmit itch signals: histaminergic vs. non-histaminergic

- Both pathways activate itch-selective C fibers[5] but each activates a separate and distinct population[2]
- Both pathways go through dorsal-root ganglion → spinal cord → spinothalamic tract (STT) → brain
  - Different tracts and different brain activation[2]

Neuronal pathways of itch:



Yosipovitch, Gil, et al. "Itch: From mechanism to (novel) therapeutic approaches." The Journal of Allergy and Clinical Immunology, vol. 142, September 2018, pp. 1375-1390. https://doi.org/10.1016/j.jaci.2018.09.005. 11 November 2018.

Image: Pruritogens stimulate unmyelinated C fibers which are divided into 2 subgroups: histaminergic and non-histaminergic. The two tracts have differences but also follow a pathway from the DRG, spinal cord, STT, and brain.[3]

Three main theories regarding itch detection and the relationship between pain and itch:

Intensity Theory:

- Interprets itch as a form of pain[2]
- Suggests that:
  - Itch and pain activate the same neurons
  - These neurons distinguish whether it is painful or itchy based on intensity
  - Weak activation of neuron → itch
  - Strong activation of neuron → pain
- Disproven by studies showing that modifying intensity did not convert itch to pain or vice versa[4]

Labeled Line Theory:

- Suggests that:
  - Itch-specific fibers transmit information to the spinal cord[2]
    - Specific set of C fibers in humans are histamine-sensitive and different from other known pain receptors[4]
- However, a later study showed pain stimuli (capsaicin) activated the C fibers that were hypothesized to be itch-specific[4]
  - Capsaicin is also unrelated to histamine[4]

Selectivity Theory:

- Suggests that:
  - There is a large population of pain receptors and a smaller population of itch-sensitive receptors within it
  - Stimulation of the smaller itch-sensitive population would generate itch
  - However, if a pain stimulus also activates the larger population, the sensation of pain would override the itch-sensitive subset of receptors[4]

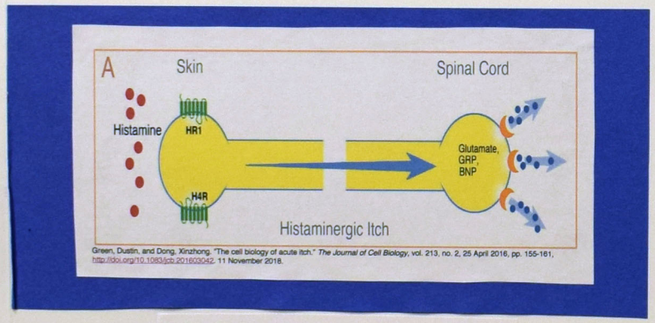


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Image: In the histaminergic pathway, histamine binds to receptors (HR1 and H4R) to transmit the itch signal. Presynaptic terminals then release glutamate, GRP, and BNP.[1]

Histaminergic Pathway:

- Histaminergic pathway is associated with acute itch
  - Released by mast cells, basophils, and keratinocytes
  - Histaminergic nerves have histamine receptors
  - When histamine is bound:
    - Phospholipase C and other signal pathways are activated
    - Neuropeptides like substance P and and CGRP released which cause the inflammation associated with itch[5]

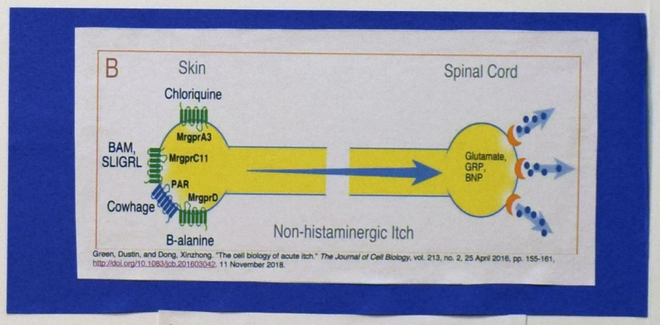

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Image: Independent of histamine, the non-histaminergic pathway evokes itch through other pruritogens like cowhage or B-alanine which bind to protein receptors. Binding of these ligands eventually results in presynaptic release of glutamate, GRP, and BNP.[1]

Non-Histaminergic Pathway:

- Non-histaminergic pathway is associated with chronic itch
  - Non-histaminergic nerves respond to pruritogens other than histamine whose receptors also activate a phospholipase signal pathway
- Cowhage (*Mucuna pruriens*)
  - The plant's spicules contain a protease that induces sensation of itch
  - Used in most research involving non-histaminergic pathway[5]

In summary:

- There is still a lot about itching that we don't know:
  - No clear model of itching as of yet although there are theories regarding pain vs. itch detection[2]
    - Intensity vs. labeled line and selectivity theories
    - Difference in species: humans and nonhuman primates vs. mice and rats[4]
  - Brain mechanisms of itch sensation unclear as well: the first studies began only around 20 years ago[3]
  - Why scratching alleviates the itch or why itching is contagious are also topics requiring further research[3]

Works Cited

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